REMARKS

Claim 19 is pending in the subject application. Applicants have hereinabove amended claim 19 to replace the term Herceptin with the term "Trastuzumab" and amended the specification to add the term "Trastuzumab". Applicants note that as of the international filing date of the subject application, i.e. as of June 9, 2000, the term "Trastuzumab" was known by those of skill in the art as the monoclonal antibody sold under the trademark HERCEPTIN. In support, applicants attach hereto copies of the following documents which show that the term HERCEPTIN was also known as Trastuzumab before June 9, 2000: (i) Barbara Sibbald (1999) *CMAJ* 161(9): 1173 (**Exhibit B**); (ii) Kollmannsberger et al. (1999) *Annals of Oncology* 10: 1393-1394 (**Exhibit C**); and (iii) product label for HERCEPTIN (Trastuzumab) (1998) Genentech (2 pages) (**Exhibit D**). Therefore, applicants maintain that these amendments do not involve any issue of new matter. Accordingly, entry of these amendments is respectfully requested such that claim 19 will be pending and under examination.

In view of these amendments and the arguments set forth below, applicants maintain that the Examiner's rejections have been overcome and respectfully request that the Examiner reconsider and withdraw same.

December 27, 2006 Advisory Action

On December 27, 2006, an Advisory Action was issued by the U.S. Patent Office in connection with the subject application. In the Advisory Action, the Examiner stated that applicants' November 30, 2006 Amendment would not be entered because it raises new issues that would require further consideration and/or search.

The Examiner stated that the amendment of claim 19 to recite the term "Herceptin" raises the new issue of 35 U.S.C. §112, second paragraph, because the term "Herceptin" is a trademark.

On May 24, 2007, Maria V. Marucci, Esq. of the undersigned attorney's office conducted a telephone interview with Examiner Bridget Bunner concerning the outstanding rejections in this application. During the May 24, 2007 telephonic interview, the Examiner stated that applicants could overcome the 35 U.S.C. §112, second paragraph, rejection set forth in the Advisory Action by submitting a declaration or petition along with evidence showing that as of the filing date of the subject application one of skill in the art would have known that the terms Herceptin and Trastuzumab referred to the same product. However, following a May 30, 2007 telephone message from Ms. Marucci, the Examiner acknowledged in a June 1, 2007 telephone message to Ms. Marucci that neither a declaration nor a petition would be required. Instead, the Examiner stated that applicants could submit the evidence as an exhibit to this response without a petition or a declaration. Applicants wish to thank the Examiner for her time.

In response, applicants submit the attached RCE and respectfully request that the Examiner enter and consider the November 30, 2006 Amendment previously submitted in connection with the subject application.

In addition, applicants without conceding the correctness of the Examiner's position in the December 27, 2006 Advisory Action and to expedite prosecution of the subject application have hereinabove amended the subject specification by adding the term Trastuzumab and amended pending claim 19 to replace the term

Herceptin with the term Trastuzumab.

Pursuant to MPEP §2163.07, "Amendments to an application which are supported in the original description are NOT new matter. I. REPHRASING. Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible. (cite omitted). The mere inclusion of dictionary or art recognized definitions known at the time of filing an application would not be considered new matter."

As set forth hereinabove, as of the international filing date of the subject application, i.e. as of June 9, 2000, the term "Trastuzumab" was known by those of skill in the art as the monoclonal antibody sold under the trademark HERCEPTIN (see Exhibits B-D attached hereto). Therefore, applicants maintain that the amendments to the specification and to claim 19 to add the art recognized term Trastuzumab to define the term Herceptin do not involve any issue of new matter.

In view of the above remarks, applicants respectfully maintain their traversal of the outstanding rejections of claim 19 set forth in the June 30, 2006 Final Office Action and December 27, 2006 Advisory Action and request that the Examiner reconsider the grounds for rejection set forth therein in view of the amendments set forth hereinabove and the remarks set forth in applicants' November 30, 2006 Amendment which was filed with the U.S. Patent Office in connection with the subject application.

Upon reconsideration applicants earnestly solicit allowance of pending claim 19.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $395.00 RCE filing fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
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Tel. No. (212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

6/4/07

John P. White
Reg. No. 28,678

Date

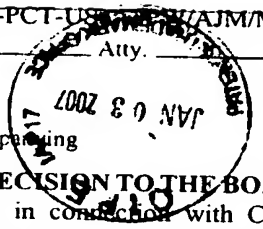
Exhibit A

Carlos Cordor.-Cardo et al.

Applicant MSK (1747) 55293-B-PCT-US/AJM/MVM

Client _____ File No. _____ Atty. _____

Date December 29, 2006



Kindly acknowledge receipt of the accompanying

NOTICE OF APPEAL FROM THE EXAMINER'S DECISION TO THE BOARD OF PATENT APPEALS AND INTERFERENCES in connection with Carlos Cordon-Cardo et al., for MARKERS FOR PROSTATE CANCER, U.S. Serial No. 10/009,861, filed December 10, 2001, including a check in the amount of $250.00 and a Certificate of Mailing dated December 29, 2006.

Date Due: December 30, 2006

by placing your receiving date stamp hereon and returning to us.

Exhibit B

Making a case for a $2700-a-month drug

Barbara Sibbald

A new class of biotherapeutic cancer drugs costs $2700 a month but its proponents make no apologies. Trastuzumab (Herceptin), the first monoclonal antibody approved for use in Canada, adds an average of 5 months to the lives of up to a third of women with metastatic breast cancer. And although the price has raised ethical questions about whether people have a right to a therapy regardless of its cost, those involved say it's not exorbitant given the expense of development and production.

Neil Cohen, a spokesman for the drug's manufacturer, California-based Genentech, Inc., says the high cost is due to the years of research and development — including a phase 3 clinical trial involving 900 patients — manufacturing costs and ongoing research into other possible uses.

Dr. Brian Leyland-Jones, a lead investigator for the trastuzumab clinical trials, says it costs between $250 and $500 million to bring a regular pharmaceutical product to market. "The costs are phenomenal," he argues. He is presently involved in another trial in which the drugs needed for 8 patients cost $250 000.

Research into monoclonal antibodies has been under way for 15 to 20 years. Rituximab (Rituxan), which targets non-Hodgkin's lymphoma, entered the US market 2 years ago but is still awaiting Health Canada approval. A 22-day course of that drug costs US$9438. Trastuzumab, the second monoclonal antibody and the first gene-directed therapy, received Health Canada approval in August.

In the US, Genentech dodges the tricky ethical issues by providing trastuzumab and its other drugs free to uninsured or underinsured patients. Over the past 12 years, Genentech has given away more than $200 million worth of its drugs.

However, that's not the case in Canada, where administrators are wondering just how much the public health care system can afford. Ontario has agreed to pay for the new breast cancer drug, and BC is following suit, but other provinces haven't made a decision yet. This uncertainty will no doubt contribute to what ethicist Margaret Somerville calls a "surge" in court challenges over withholding medically necessary treatment.

Somerville, the director of the Centre for Medicine, Ethics and Law at McGill University, agrees that Canada's health care system can't pay for everything. "We can't afford to offer every treatment to everyone . . . but we have always lived with the myth that we can." She says the soaring litigation is a sign that this "myth is being shattered."

But the cost shouldn't override the "huge promise" inherent in trastuzumab and this whole new family of drugs, says Leyland-Jones, professor and chair of McGill's Department of Oncology. "This is just the tip of the iceberg," he says, since other drugs based on monoclonal antibody drugs are now being developed. "They are discriminate, selective drugs aimed at specific genetic targets," he says. "It's entirely different from chemotherapy or radiation."

Side effects are negligible. Leyland-Jones says some patients report chills and fevers the day of their first infusion, but nothing more. "Patients said it's like taking water," he said. The drug is administered weekly.

Leyland-Jones says cancer therapy has been evolving since the end of the last century. The first advances were in surgery, followed by the introduction of radiation. Those developments were followed by the arrival of chemotherapy in the 1940s. This latest step is "fourth-generation therapy — the selective gene-targeted therapies."

Trastuzumab has been in the making since 1986, when American oncologist Dennis Slamon and German molecular biologist Axel Ullrich discovered that as many as 35% of breast tumours contained a mutation in the HER2 (human epidermal growth factor receptor 2) oncogene (also known as c-*erb*B2). This mutation causes breast cells to make abnormally high amounts of the HER2 protein (overexpression), which appears as a receptor on the surface of the cell. These receptors receive chemical signals from the body to grow, stimulating the cells to grow out of control. Ullrich and Slamon also discovered an antibody that clung to the HER2 protein, marking the cancer cells for death. Genentech owns the rights to the antibody.

The drug was extensively tested in a 4-arm study: trastuzumab alone; trastuzumab with the chemotherapy combination doxorubicin and cyclophosphamide; trastuzumab with chemotherapy including paclitaxel (Taxol); and paclitaxel alone. The women taking trastuzumab combined with doxorubicin and cyclophosphamide had an increased (27%) risk of cardiac dysfunction, including impaired left ventricular function and heart failure. However, trastuzumab combined with chemotherapy including paclitaxel was found to improve survival by an average of 5 months over chemotherapy alone in women with metastatic breast cancer and overexpression of the HER2 protein.

Barbara Sibbald is CMAJ's Associate Editor, News and Features.

Exhibit C

Annals of Oncology 10: 1393–1395, 1999.

Letters to the editor

Friedreich's ataxia and intrathecal chemotherapy in a patient with lymphoblastic lymphoma

Friedreich's ataxia (FA) is the most common spino-cerebellar degeneration of unknown etiology, with signs and symptoms developing from 18 months to 24 years of age. Common neurological signs are limb and truncal ataxia, dysarthria, areflexia of the lower extremities; pyramidal signs, loss of position and vibratory sense evolve gradually. Distal amyotrophy, horizontal nystagmus and optic atrophy are less common. Non-neurological features include kyphoscoliosis, pes cavus and cardiomyopathy. Pathological features of FA are narrowed spinal cord with cell loss and gliosis in the spinocerebellar and corticospinal tracts and in the posterior column, Clarke's column and depleted dorsal root ganglia, such as cranial nerve nuclei VIII, X and XII. Large myelinated peripheral nerves are lost, and myocardial fibers degenerated.

We treated a 16-year-old male affected by FA, who suffers from a stage IIA bulky lymphoblastic T-cell non-Hodgkin's lymphoma with mediastinal presentation. FA-related signs were kyphoscoliosis, hypertrophical cardiomyopathy and cerebellar mild ataxia. A cerebral magnetic resonance showed a moderate spino-bulbar atrophy.

At the time of diagnosis, because of rapidly worsening dyspnea, mediastinal radiotherapy was performed in another hospital and, after partial recovery, the patient was admitted to our Department to start systemic chemotherapy.

Although lumbar puncture did not find malignant cells, we performed a prophylactic intrathecal administration with Methotrexate 10 mg, ara-C 70 mg and hydrocortisone 30 mg. Concomitant systemic chemotherapy with a five-drug regimen (adriamycin 25 mg/m^2 dd 1–8, vincristine 1 mg dd 1–8, cyclophosphamide 600 mg dd 1–8, prednisone 50 mg dd 1–>8 and methotrexate 1.5 g/m^2 d 15) was also started. Six cycles of intrathecal and systemic chemotherapy were administered.

No acute side effects appeared during or after the intrathecal treatments, nor any neurological complications after over two years' follow-up; neurological manifestations related to FA are unchanged and the patient is still in complete remission.

We think it is very important to report this single experience, considering that no data are available about the feasibility and toxicity of intrathecal chemotherapy in patients affected by central nervous system degenerations, probably because of the extreme rarity of this combined health problem.

T. De Pas,[1] G. Martinelli,[1] F. De Braud,[1] F. Peccatori,[1] C. Catania,[1] M. S. Aapro[2] & A. Goldhirsch[1]
[1]*European Institute of Oncology, Milan, Italy;* [2]*Clinique de Genolier, Switzerland*

Cisplatin-refractory, HER2/neu-expressing germ-cell cancer: Induction of remission by the monoclonal antibody Trastuzumab

Patients with cisplatin-refractory germ-cell cancer or relapse following cisplatin-based first-line therapy exhibit a very poor prognosis. Only 15%–20% of patients are long-term survivors after standard- or high-dose salvage chemotherapy [1].

The HER2/neu receptor has been shown to be expressed in a variety of tumors, including breast, prostate and ovarian cancer. A recently published report indicates that about 30% of all refractory germ-cell cancers may overexpress HER2/neu [2]. Trastuzumab (Herceptin®), a mouse/human IgG1 chimeric antibody not only binds to the HER2/neu receptor and subsequently inhibits cell proliferation, but is also able to mediate an antibody-dependent, cell-mediated cytotoxicity *in vitro* [3]. To date, trastuzumab has shown a marked clinical activity in patients with HER2/neu positive breast cancer.

We report a 51-year-old male with heavily pretreated, cisplatin-refractory and HER2/neu overexpressing germ-cell cancer in whom a partial remission was achieved with Trastumab therapy.

The patient had undergone a right-sided inguinal orchiectomy, as well as a retroperitoneal lymph node dissection for embryonal carcinoma in 1982. In April 1993 he was found to have paraaortal lymph node metastases. During the following six years, the patient suffered four additional relapses, all located in the retroperitoneum and in the lungs. Treatment consisted of various chemotherapy regimens, including four cisplatin-based regimens. In addition, retroperitoneal and lung metastases were repeatedly resected.

In May 1998, the patient was referred to our department for further therapy. Staging procedures revealed lung metastases and a retroperitoneal mass, as well as an elevated AFP-level. The patient received several additional salvage chemotherapy regimens, including paclitaxel and gemcitabine, both of which are known to be potentially active in metastatic GCT [1].

However, remission could not be induced and the AFP-level rose constantly. At this time, the lung metastases specimen, resected in 1998 was examined for HER2/neu expression.

Immunohistochemical staining (ABC-test; Novocasta Inc.) showed a significant HER2/neu overexpression with 90%–100% of all tumor cells being HER2/neu positive (Figure 1).

After obtaining informed consent, the patient was started on experimental treatment with trastuzumab. A loading dose of 4 mg/kg body weight was administered in week 1, followed by 2 mg/kg body weight once weekly. AFP-level at the start of trastuzumab was 6000 KU/l. The AFP-level began to decline after the first administration of trastuzumab and declined to 700 KU/l after seven weeks of therapy.

Trastuzumab therapy was very well tolerated with no side effects. Repeat echocardiograms showed no signs of cardiac toxicity. Overall, the patient received eight weeks of therapy. Unfortunately, the AFP-level started to rise following two weeks rest and the patients was started on an alternative palliative chemotherapy regimen.

Despite the high cure rate achievable in testicular cancer

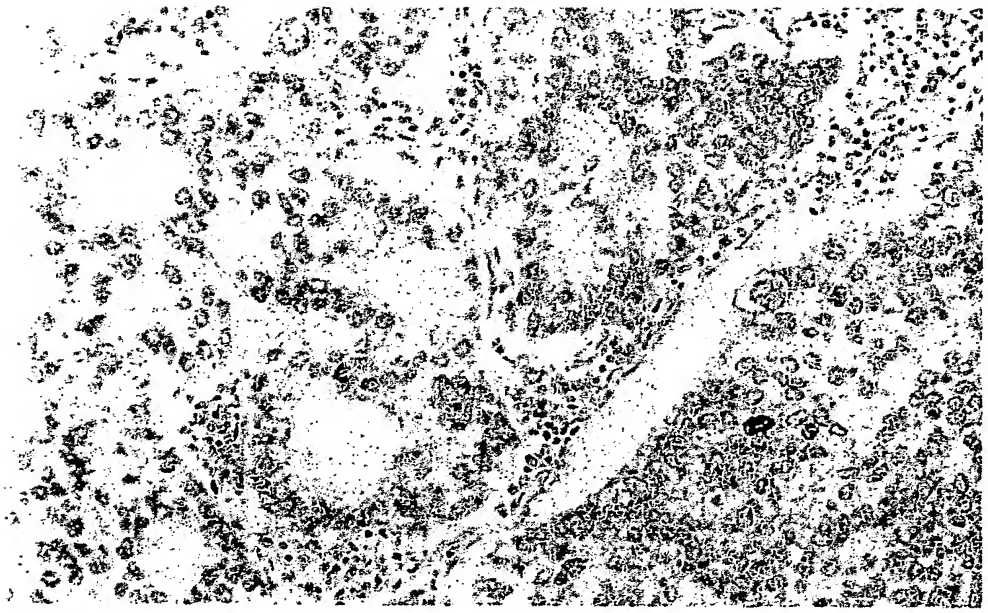


Figure 1. Lung metastases specimen: significant overexpression of HER2/neu (Immunhistochemical staining ABC-test; Novocasta Inc.).

patients, a small number remain who cannot be cured with current treatment strategies. For those patients, new treatment options must be explored. Accordingly, HER2/neu may serve as a new target in those patients who overexpress the c-erbB oncogene. The present observation indicates that the use of molecular targeted therapy should be further investigated, possibly in combination with chemotherapy, in order to fully define its role not only in the treatment of both refractory and chemosensitive testicular cancer patients, but also in patients with other tumors overexpressing HER2/neu.

C. Kollmannsberger,[1] H. Preßler,[2] F. Mayer,[1] L. Kanz[1] & C. Bokemeyer[1]

[1]*Department of Hematology/Oncology, University of Tuebingen Medical Center;* [2]*Department of Pathology, University of Tübingen, Tübingen, Germany*

References

1. Bokemeyer C, Kollmannsberger C, Harstrick A et al. Treatment of patients with cisplatin refractory testicular germ-cell cancer. Int J Cancer 1999 (in press).
2. Henley J, Einhorn LH. C-erbB-2 (Her-2-neu) overexpression in recurrent germ-cell tumors. Proc Am Soc Clin Oncol 1999; 18: 341a (Abstr 1313).
3. Klapper LN, Vaisman N, Hurwitz E et al. A subclass of tumor-inhibitory monoclonal antibodies to Erb2/HER2 blocks crosstalk with growth factor receptor. Oncogene 1997; 14: 2099–109.

Hepatic toxicity from cyclophosphamide, methotrexate, fluorouracil (CMF regimen)

CMF combination chemotherapy is one of the most effective and safe regimens used as adjuvant systemic treatment for breast cancer. There are limited data in the literature of hepatic toxicity from adjuvant chemotherapy. Moreover, there are no published reports focusing on liver toxicity from combination chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF), with M and F given i.v. on days 1 and 8 every four weeks (classical CMF). We therefore, evaluated retrospectively serial liver function tests (LFT) of 264 patients treated with adjuvant CMF after surgery for early breast cancer, to asses the incidence and severity of hepatic toxicity.

Patients were treated at our institution from 11 July 1995 to 26 July 1999 according to the following regimen (oral cyclophosphamide 100 mg/m^2 (Endoxan-Asta®; Asta Medica, Italy), days 1–14, methotrexate 40 mg/m^2 (Methotrexate®; Teva, Italy) and 5-fluorouracil 600 mg/m^2 (Fluoro-Uracile®; Teva, Italy) i.v., both on days die 1, 8). Each patient had a baseline history and a physical examination, serum alkaline phosphatase, transaminases (SGOT, SGPT), bilirubin total, lactate dehydrogenase determinations, a chest X-ray, a 99mTC phosphate bone scan and a liver ultrasound. Liver functions tests were repeated at least every eight weeks. All patients received Granisetron and Dexametazone as prophylaxis against nausea and vomiting, but no other medicines were routinely given. All patients were tested for HBV markers and anti-HCV antibodies at presentation (three patients were positive for HBsAg and anti-HBsAg and three for HCV). Median age was 49 (range 25–74 years). No evidence of previous history of liver disease or evidence of functional liver abnormality was detected at baseline. Two patients previously received neoadjuvant chemotherapy and ninety-four patients have received four cycles of AC or EC schedule (doxorubicin 60 mg/m^2 (Adriblastina®;

Exhibit D

HERCEPTIN®
Trastuzumab

WARNING
CARDIOMYOPATHY:
HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with HERCEPTIN. Discontinuation of HERCEPTIN treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received HERCEPTIN in combination with anthracyclines and cyclophosphamide. (See WARNINGS.)

DESCRIPTION
HERCEPTIN (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor2 protein, HER2.[1,2] The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary) [CHO] suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

HERCEPTIN is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial of HERCEPTIN contains 440mg Trastuzumab, 9.9mg L-histidine HCl, 6.4mg L-histidine, 400 mg α,α-trehalose dihydrate, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection, (BWFI) USP, containing 1.1%benzyl alcohol as a preservative, yields 21mL of a multi-dose solution containing 21mg/mL Trastuzumab, at a pH of approximately 6.

CLINICAL PHARMACOLOGY
General
The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185kDa, which is structurally related to the epidermal growth factor receptor.[1] HER2 protein overexpression is observed in 25%-30% of primary breast cancers. HER2 protein overexpression can be determined using an immunohistochemistry-based assessment of fixed tumor blocks.[3]

Trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.[4-6]

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC).[7,8] *In vitro*, HERCEPTIN-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Pharmacokinetics
The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 microgram/mL.

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range = 1 to 32 days) was observed. Between weeks 16 and 32, Trastuzumab serum concentrations reached a steady-state with a mean trough and peak concentrations of approximately 79microgram/mL and 123 microgram/mL, respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2 overexpressing tumors. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of Trastuzumab by week 6.

Data suggest that the disposition of Trastuzumab is not altered based on age or serum creatinine (up to 2.0 mg/dL). No formal interaction studies have been performed.

Mean serum trough concentrations of Trastuzumab, when administered in combination with paclitaxel, were consistently elevated approximately 1.5-fold as compared with serum concentrations of Trastuzumab used in combination with anthracycline plus cyclophosphamide. In primate studies, administration of Trastuzumab with paclitaxel resulted in a reduction in Trastuzumab clearance. Serum levels of Trastuzumab in combination with cisplatin, doxorubicin or epirubicin plus cyclophosphamide did not suggest any interactions; no formal drug interaction studies were performed.

CLINICAL STUDIES
The safety and efficacy of HERCEPTIN were studied in a randomized, controlled clinical trial in combination with chemotherapy (469patients) and an open-label single agent clinical trial (222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpressthe HER2 protein. Patients were eligible if they had 2+ or 3+ levels of overexpression (based on a 0-3+ scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

A multicenter, randomized, controlled clinical trial was conducted in 469patients with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Patients were randomized to receive chemotherapy alone or in combination with HERCEPTIN given intravenously as a 4 mg/kg loading dose followed by weekly doses of HERCEPTIN at 2mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). Compared with patients in the AC subgroups (n = 281), patients in the paclitaxel subgroups (n = 188) were more likely to have had the following: poor prognostic factors (premenopausal status, estrogen or progesterone receptor negative tumors, positive lymph nodes), prior therapy (adjuvant chemotherapy, myeloablative chemotherapy, radiotherapy), and a shorter disease-free interval.

Compared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemotherapy experienced a significantly longer time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate. (See Table1.) These treatment effects were observed both in patients who received HERCEPTIN plus paclitaxel and in those who received HERCEPTIN plus AC, however the magnitude of the effects was greater in the paclitaxel subgroup. The degree of HER2 overexpression was a predictor of treatment effect. (See CLINICAL STUDIES: *HER2 protein overexpression.*)

Table 1
Phase III Clinical Efficacy in First-Line Treatment

	Combined Results HERCEPTIN + All Chemotherapy	All Chemotherapy	Paclitaxel subgroup HERCEPTIN + Paclitaxel	Paclitaxel	AC subgroup HERCEPTIN + AC[a]	AC
	(n = 235)	(n = 234)	(n = 92)	(n = 96)	(n = 143)	(n = 138)
Primary Endpoint						
Time to Progression[b,c]						
Median (months)	7.2	4.5	6.7	2.5	7.6	5.7
95% confidence interval	6.9, 8.2	4.3, 4.9	5.2, 9.9	2.0, 4.3	7.2, 9.1	4.6, 7.1
p-value (log rank)	<0.0001		<0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]						
Rate (percent)	45	29	38	15	50	38
95% confidence interval	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value (χ2-test)	<0.001		<0.001		0.10	
Duration of Response[b,c]						
Median (months)	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% quantile	5.5, 14.8	3.9, 8.5	5.1, 11.0	3.7, 7.4	5.8, 14.8	4.5, 8.5
1-Year Survival[c]						
Percent alive	79	68	73	61	83	73
95% confidence interval	74, 84	62, 74	66, 80	51, 71	77, 89	66, 82
p-value (Z-test)	<0.01		0.08		0.04	

[a] AC = anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate

HERCEPTIN was studied as a single agent in a multicenter, open-label, single-arm clinical trial inpatients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of HERCEPTIN® (Trastuzumab) at 2mg/kg IV. The ORR (complete response+ partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes. The degree of HER2 overexpression was a predictor of treatment effect. (See CLINICAL STUDIES. *HER2 protein overexpression.*)

HER2 protein overexpression
Relationship to Response: In the clinical studies described, patient eligibility was determined by testing tumor specimens for overexpression of HER2 protein. Specimens were tested with a research-use-only immunohistochemical assay (referred to as the Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+ with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened).

Data from both efficacy trials suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+). (See Table 2.)

Table 2
Treatment Effect versus Level of HER2 Expression

	Single-Arm Trial HERCEPTIN	Treatment Subgroups in Randomized Trial HERCEPTIN + Paclitaxel	Paclitaxel	HERCEPTIN + AC	AC
Overall Response Rate					
2+ overexpression	4% (2/50)	21% (5/24)	16% (3/19)	40% (14/35)	43% (18/42)
3+ overexpression	17% (29/172)	44% (30/68)	14% (11/77)	53% (57/108)	36% (35/96)
Median time to progression (months) (95% CI)					
2+ overexpression	N/A*	4.4 (2.2, 6.6)	3.2 (2.0, 5.6)	7.8 (6.4, 10.1)	7.1 (4.8, 9.8)
3+ overexpression	N/A*	7.1 (6.2, 12.0)	2.2 (1.8, 4.3)	7.3 (7.1, 9.2)	4.9 (4.5, 6.9)

* N/A = Not Assessed

Immunohistochemical Detection: In clinical trials, the Clinical Trial Assay (CTA) was used for immunohistochemical detection of HER2 protein overexpression. The DAKO HercepTest™, another immunohistochemical test for HER2 protein overexpression, has not been directly studied for its ability to predict HERCEPTIN treatment effect, but has been compared to the CTA on over 500 breast cancer histology specimens obtained from the National Cancer Institute Cooperative Breast Cancer Tissue Resource. Based upon these results and an expected incidence of 33% of 2+ or 3+ HER2 overexpression in tumors from women with metastatic breast cancer, one can estimate the correlation of the HercepTest™ results with CTA results. Of specimens testing 3+ (strongly positive) on the HercepTest™, 94% would be expected to test at least 2+ on the CTA (i.e., meeting the study entry criterion) including 82% which would be expected to test 3+ on the CTA (i.e., the reading most associated with clinical benefit). Of specimens testing 2+ (weakly positive) on the HercepTest™, only 34% would be expected to test at least 2+ on the CTA, including 14% which would be expected to test 3+ on the CTA.

INDICATIONS AND USAGE
HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. HERCEPTIN should only be used in patients whose tumors have HER2 protein overexpression. (See CLINICAL STUDIES: *HER2 protein overexpression* for information regarding HER2 protein testing and the relationship between the degree of overexpression and the treatment effect.)

CONTRAINDICATIONS
None known.

WARNINGS
Cardiotoxicity:
Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S_3 gallop, or reduced ejection fraction, have been observed in patients treated with HERCEPTIN. Congestive heart failure associated with HERCEPTIN therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke. The clinical status of patients in the trials who developed congestive heart failure were classified for severity using the New York Heart Association classification system (I—IV, where IV is the most severe level of cardiac failure). (SeeTable 3.)

Table 3
Incidence and Severity of Cardiac Dysfunction

	HERCEPTIN® alone n = 213	HERCEPTIN + Paclitaxel[b] n = 91	Paclitaxel[b] n = 95	HERCEPTIN + Anthracycline + cyclophosphamide[b] n = 143	Anthracycline + cyclophosphamide[b] n = 135
Any Cardiac Dysfunction	7%	11%	1%	28%	7%
Class III-IV	5%	4%	1%	19%	3%

[a] Open-label, single-agent Phase 2 study (94% received prior anthracyclines).
[b] Randomized Phase III study comparing chemotherapy plus HERCEPTIN to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel.

Candidates for treatment with HERCEPTIN should undergo thorough baseline cardiac assessment including history and physical exam and one or more of the following: EKG, echocardiogram, and MUGA scan. There are no data regarding the most appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring may not identify all patients who will develop cardiac dysfunction.

Extreme cautionshould be exercised in treating patients with pre-existing cardiac dysfunction.

Patients receiving HERCEPTIN should undergo frequent monitoring for deteriorating cardiac function.

The probability of cardiac dysfunction was highest in patients who received HERCEPTIN concurrently with anthracyclines. The data suggest that advanced age may increase the probability of cardiac dysfunction.

Pre-existing cardiac disease or prior cardiotoxic therapy (e.g., anthracycline or radiation therapy to the chest) may decrease the ability to tolerate HERCEPTIN therapy; however, the data are not adequate to evaluate the correlation between HERCEPTIN-induced cardiotoxicity and these factors.

Discontinuation of HERCEPTIN therapy should be strongly considered in patients who develop clinically significant congestive heart failure. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy often including discontinuation of HERCEPTIN. The safety of continuation or resumption of HERCEPTIN in patients who have previously experienced cardiac toxicity has not been studied. There are insufficient data regarding discontinuation of HERCEPTIN therapy in patients with asymptomatic decreases in ejection fraction; such patients should be closely monitored for evidence of clinical deterioration.

PRECAUTIONS
General: HERCEPTIN therapy should be used with caution in patients with known hypersensitivity to Trastuzumab, Chinese Hamster Ovary cell proteins, or any component of this product.

Drug Interactions: There have been no formal drug interaction studies performed with HERCEPTIN in humans. Administration of paclitaxel in combination with HERCEPTIN resulted in a two-fold decrease in HERCEPTIN clearance in a non-human primate study and in a 1.5-fold increase in HERCEPTIN serum levels in clinical studies (see Pharmacokinetics).

Benzyl Alcohol: For patients with a known hypersensitivity to benzyl alcohol (the preservative in Bacteriostatic Water for Injection) reconstitute HERCEPTIN® (Trastuzumab) with Sterile Water for Injection (SWFI), USP. DISCARD THE SWFI-RECONSTITUTED HERCEPTIN VIAL FOLLOWING A SINGLE USE.

Immunogenicity: Of 903 patients who have been evaluated, human anti-human antibody (HAHA) to Trastuzumab was detected in onepatient, who had no allergic manifestations.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: HERCEPTIN has not been tested for its carcinogenic potential.

Mutagenesis: No evidence of mutagenic activity was observed in Ames tests using six different test strains of bacteria, with and without metabolic activation, at concentrations of up to 5000 μg/mL Trastuzumab. Human peripheral blood lymphocytes treated *invitro* at concentrations of up to 5000 μg/plate Trastuzumab, with and without metabolic activation, revealed no evidence of mutagenic potential. In an *invivo* mutagenic assay (the micronucleus assay), no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg Trastuzumab.

Impairment of Fertility: A fertility study has been conducted in female cynomolgus monkeys at doses up to 25times the weekly human maintenance dose of 2mg/kg HERCEPTIN and has revealed no evidence of impaired fertility.

Pregnancy Category B: Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg HERCEPTIN and have revealed no evidence of impaired fertility or harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation.[9] Placental transfer of HERCEPTIN during the early (Days20- 50 of gestation) and late (Days120-150 of gestation) fetal development period was observed in monkeys. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: A study conducted in lactating cynomolgus monkeys at doses 25times the weekly human maintenance dose of 2mg/kg HERCEPTIN demonstrated that Trastuzumab is secreted in the milk. The presence of Trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 3 months of age. It is not known whether HERCEPTIN is excreted in human milk. Because human IgG is excreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during HERCEPTIN therapy and for 6 months after the last dose of HERCEPTIN.

Pediatric Use: The safety and effectiveness of HERCEPTIN in pediatric patients have not been established.

Geriatric Use: HERCEPTIN has been administered to 133 patients who were 65 years of age or over. The risk of cardiac dysfunction may be increased in geriatric patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients.

ADVERSE REACTIONS

A total of 958 patients have received HERCEPTIN alone or in combination with chemotherapy. Data in the table below are based on the experience with the recommended dosing regimen for HERCEPTIN in the randomized controlled clinical trial in 234 patients who received HERCEPTIN in combination with chemotherapy and four open-label studies of HERCEPTIN as a single agent in 352 patients at doses of 10—500 mg administered weekly.

Cardiac Failure/Dysfunction: For a description of cardiac toxicities, see WARNINGS.

Anemia and Leukopenia: An increased incidence of anemia and leukopenia was observed in the treatment group receiving HERCEPTIN and chemotherapy, especially in the HERCEPTIN and ACsubgroup, compared with the treatment group receiving chemotherapy alone. The majority of these cytopenic events were mild or moderate in intensity, reversible, and none resulted in discontinuation of therapy with HERCEPTIN.

Hematologic toxicity is infrequent following the administration of HERCEPTIN as a single agent, with an incidence of GradeIII toxicities for WBC, platelets, hemoglobin all<1%. No GradeIV toxicities were observed.

Diarrhea: Of patients treated with HERCEPTIN as a single agent, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving HERCEPTIN in combination with chemotherapy.

Infection: An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, was observed in patients receiving HERCEPTIN in combination with chemotherapy.

Infusion-Associated Symptoms: During the first infusion with HERCEPTIN, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of HERCEPTIN infusion). HERCEPTIN discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash, and asthenia. The symptoms occurred infrequently with subsequent HERCEPTIN infusions.

Table 4
Adverse Events Occurring in ≥ 5% of Patients or at Increased Incidence in the HERCEPTIN Arm of the Randomized Study (Percent of Patients)

	Single Agent n = 352	HERCEPTIN + Paclitaxel n = 91	Paclitaxel Alone n = 95	HERCEPTIN + AC n = 143	AC Alone n = 135
Body as a Whole					
Pain	47	61	62	57	42
Asthenia	42	62	57	54	55
Fever	36	49	23	56	34
Chills	32	41	4	35	11
Headache	26	36	28	44	31
Abdominal pain	22	34	22	23	18
Back pain	22	34	30	27	15
Infection	20	47	27	47	31
Flu syndrome	10	12	5	12	6
Accidental injury	6	13	3	9	4
Allergic reaction	3	8	2	4	2
Cardiovascular					
Tachycardia	5	12	4	10	5
Congestive heart failure	7	11	1	28	7
Digestive					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	26
Hemic & Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Nervous					
Insomnia	14	25	13	29	15
Dizziness	13	22	24	24	18
Paresthesia	9	48	39	17	11
Depression	6	12	13	20	12
Peripheral neuritis	2	23	16	2	2
Neuropathy	1	13	5	4	4
Respiratory					
Cough increased	26	41	22	43	29
Dyspnea	22	27	26	42	25
Rhinitis	14	22	5	22	16
Pharyngitis	12	22	14	30	18
Sinusitis	9	21	7	13	6
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	<1
Urogenital					
Urinary tract infection	5	18	14	13	7

Other serious adverse events
The following other serious adverse events occurred in at least one of the 958 patients treated with HERCEPTIN® (Trastuzumab):

Body as a Whole: cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia

Cardiovascular: vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock arrhythmia

Digestive: hepatic failure, gastroenteritis, hematemesis, ileus, intestinal obstruction, colitis, esophageal ulcer, stomatitis, pancreatitis, hepatitis

Endocrine: hypothyroidism

Hematological: pancytopenia, acute leukemia, coagulation disorder, lymphangitis

Metabolic: hypercalcemia, hypomagnesemia, hyponatremia, hypoglycemia, growth retardation, weight loss

Musculoskeletal: pathological fractures, bone necrosis, myopathy

Nervous: convulsion, ataxia, confusion, manic reaction

Respiratory: apnea, pneumothorax, asthma, hypoxia, laryngitis

Skin: herpes zoster, skin ulceration

Urogenital: hydronephrosis, kidney failure, cervical cancer, hematuria, hemorrhagic cystitis, pyelonephritis

OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 500 mg have not been tested.

DOSAGE AND ADMINISTRATION

Usual Dose
The recommended initial loading dose is 4 mg/kg Trastuzumab administered as a 90-minute infusion. The recommended weekly maintenance dose is 2 mg/kg Trastuzumab and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. HERCEPTIN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS** (see ADMINISTRATION).

Preparation for Administration
Use appropriate aseptic technique. Each vial of HERCEPTIN should be reconstituted with 20mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multi-dose solution containing 21 mg/mL Trastuzumab. Immediately upon reconstitution with BWFI, the vial of HERCEPTIN must be labeled in the area marked "Do not use after:" with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, HERCEPTIN must be reconstituted with Sterile Water for Injection (see PRECAUTIONS). HERCEPTIN WHICH HAS BEEN RECONSTITUTED WITH SWFI MUST BE USED IMMEDIATELY AND ANY UNUSED PORTION DISCARDED. USE OF OTHER RECONSTITUTION DILUENTS SHOULD BE AVOIDED.

Determine the number of mg of Trastuzumab needed, based on a loading dose of 4 mg Trastuzumab/kg body weight or a maintenance dose of 2 mg Trastuzumab/kg body weight. Calculate the volume of 21 mg/mL Trastuzumab solution and withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9%sodium chloride, USP. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between HERCEPTIN and polyvinylchloride or polyethylene bags have been observed.

Administration
Treatment may be administered in an outpatient setting by administration of a 4 mg/kg Trastuzumab loading dose by intravenous (IV) infusion over 90 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** Patients should be observed for fever and chills or other infusion-associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated, subsequent weekly doses of 2 mg/kg Trastuzumab may be administered over 30minutes.

HERCEPTIN should not be mixed or diluted with other drugs. HERCEPTIN infusions should not be administered or mixed with Dextrose solutions.

Stability and Storage
Vials of HERCEPTIN are stable at 2—8°C (36—46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of HERCEPTIN reconstituted with BWFI, as supplied, is stable for 28days after reconstitution when stored refrigerated at 2—8°C (36—46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28days. If unpreserved SWFI (not supplied) is used, the reconstituted HERCEPTIN solution should be used immediately and any unused portion must be discarded. DO NOT FREEZE HERCEPTIN THAT HAS BEEN RECONSTITUTED.

The solution of HERCEPTIN for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride for Injection, USP, may be stored at 2—8°C (36—46°F) for up to 24 hours prior to use. Diluted HERCEPTIN has been shown to be stable for up to 24 hours at room temperature (2—25°C). However, since diluted HERCEPTIN contains no effective preservative, the reconstituted and diluted solution should be stored refrigerated (2—8°C).

HOW SUPPLIED

HERCEPTIN is supplied as a lyophilized, sterile powder containing 440mg Trastuzumab per vial under vacuum.

Each carton contains one vial of 440mg HERCEPTIN® (Trastuzumab) and one 30mL vial of Bacteriostatic Water for Injection, USP, 1.1% benzyl alcohol. NDC 50242-134-60.

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